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(54) **Title of Invention: Application of Renin-Inhibiting Peptides as Agents Against Retroviruses**

(57) **Abstract:** The invention concerns the application of known renin-inhibiting peptides as antiviral agents in human and animal medicine.

Application of renin-inhibiting peptides as agents against retroviruses.

This invention concerns the application of known renin-inhibiting peptides as antiviral agents in human and animal medicine.

It is already known that the renin-inhibiting peptides listed below affect the circulation and can be used to treat high blood pressure and cardiac insufficiency [see EP 01 04 041; EP 01 44 290; EP 00 77 029; EP 00 81 783; EP 01 11 268; EP 00 77 028; EP-A2 01 72 347; EP-A2 01 81 071; EP-A2 02 11 586; EP-A2 02 23 437; EP-A2 01 32 304; EP-A1 01 18 223].

Now it has been discovered that peptides of the general formula (I)

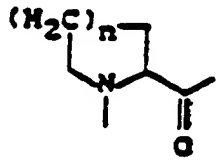
X-A-B-D-Y-E-F-Z (I)

in which

X is hydrogen,
a straight or branched alkyl chain, alkylsulfonyl or alkoxycarbonyl with up to 10 carbon atoms
or a group with the formula -COR^1
wherein

R^1 is a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by hydroxy, amino or aryl with 6 to 10 carbon atoms, phenylsulfonyl, tolylsulfonyl, or naphthyl, or an amine-protecting group;

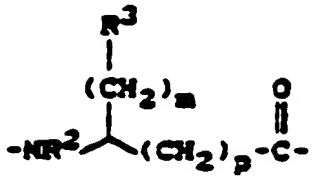
A is a direct linkage,
or
a residue of the formula



(a)

in which n is the number 1 or 2,

or a group of the formula



(b)

in which

m is a number 0, 1, 2, 3, or 4,

p is a number 0 or 1,

R^2 is hydrogen, a straight or branched alkyl chain with up to 8 carbon atoms, naphthyl or an amine-protecting group,

R^3 is hydrogen, naphthyl, halogen, carboxy, a straight or branched alkyl or alkylthio with up to 8 carbon atoms, which may be substituted by mercapto, alkylcarbonyl with up to 8 carbon atoms, hydroxy or halogen, or

a group of the formula $-CH_2-NHR^4$ in which

R^4 is hydrogen, a straight or branched alkyl or alkylsulfonyl with up to 8 carbon atoms, phenylsulfonyl or an amine-protecting group,

guanidino, indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, which may be substituted by R^4, in which R^4 has the meaning stated above,

aryl with 6 to 10 carbon atoms, which may have up to three identical or different substituents of straight or branched alkyl or alkoxy with up to 8 carbon atoms, halogen, hydroxy, nitro, or by a group with the formula

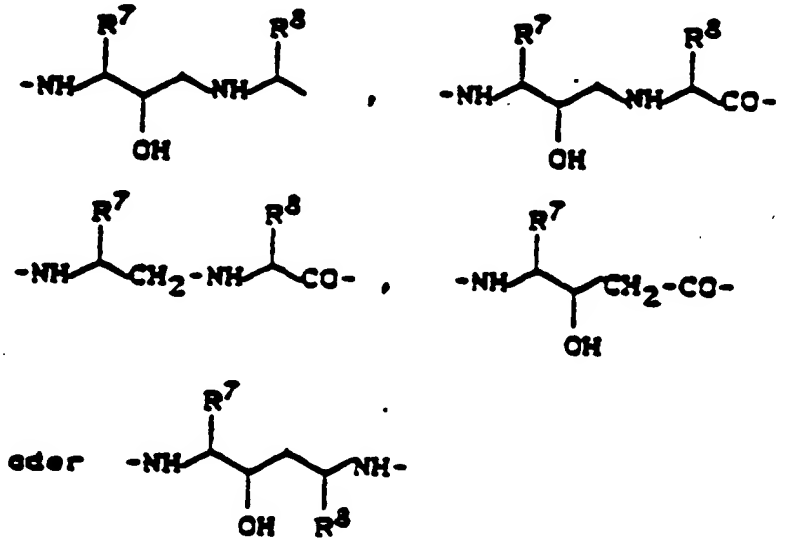
$-NR^5R^6$ in which

R^5 and R^6 are the same or different, and are hydrogen or a straight or branched alkyl with up to 8 carbon atoms,

B, E, and F are the same or different, and have the meaning stated above for A, and are the same as A or different from it, in the D form, L form, or the DL isomeric mixture, preferably in the L form, and

D has the meaning stated above for A and is the same as A or different from it, in its D form, L form, or the DL mixture, with the provision that D may not represent a direct linkage and may not represent Asparagine (Asp),

Y is a group of the formula



(c)

(oder = or)

in which

R^7 is a straight or branched alkyl chain with up to 12 carbon atoms, which may be substituted by cycloalkyl with 3 to 8 carbon atoms, aryl with 6 to 10 carbon atoms, halogen, hydroxyl, nitro, or a saturated or unsaturated 5 to 7 membered heterocycle with up to 4 heteroatoms from the series oxygen, sulfur or nitrogen,

or

aryl with 6 to 10 carbon atoms, which may be substituted by halogen, nitro, hydroxyl, cyano, straight or branched alkyl or alkoxy with up to 8 carbon atoms, or by a group with the formula $-NR^5R^6$, in which

R^5 and R^6 have the meanings stated above,

R^8 is hydrogen,

straight or branched alkyl with up to 8 carbon atoms, which may be substituted by hydroxy, cycloalkyl with 3 to 8 carbon atoms, and/or aryl with 6 to 10 carbon atoms which itself may be substituted by nitro, cyano or hydroxy,

Z is an amine-protecting group,

a straight or branched alkyl or alkoxy with up to 10 carbon atoms, which may be substituted by hydroxy, phenyl or pyridyl,

or

a group of the formula $-NR^9R^{10}$ or $-COR^{11}$ in which

R^9 and R^{10} are the same or different and are

hydrogen,

straight or branched alkyl or alkenyl with up to 10 carbon atoms, which may be substituted by pyridyl or hydroxy,

or

a saturated 5 to 7-membered heterocycle with up to 3 heteroatoms from the series Sulfur, oxygen or nitrogen, which may be substituted by benzyl or phenyl,

R^{11} is a straight or branched alkyl with up to 8 carbon atoms, which may be substituted by pyridyl or by a group of the formula $-NR^9R^{10}$, in which

R^9 and R^{10} have the meanings stated above,

or

adamantyl or a saturated or unsaturated 7-membered heterocycle with up to 3 heteroatoms from the series oxygen, sulfur or nitrogen, which may be substituted by benzyl have not only the well-known renin-inhibiting action but also good action against retroviruses.

As used in this invention, amino-protecting groups are the usual amino-protecting groups used in peptide chemistry.

They include, preferably:
benzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, dichlorobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, isopentoxycarbonyl, hexoxycarbonyl, cyclohexoxycarbonyl, octoxycarbonyl, 2-ethylhexoxycarbonyl, 2-iodohexoxycarbonyl, 2-bromoethoxycarbonyl, 2-chloroethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, benzhydryloxycarbonyl, bis-(4-methoxyphenyl)methoxycarbonyl, phenacyloxycarbonyl, 2-trimethylsilylethoxycarbonyl, 2-(di-n-butyl-methylsilyl)ethoxycarbonyl, 2-triphenylsilylethoxycarbonyl, 2-(dimethyl-tert-butylsilyl)ethoxycarbonyl, menthyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, phenoxycarbonyl, tolyloxycarbonyl, 2,4-dinitrophenoxycarbonyl, 4-nitrophenoxycarbonyl, 2,4,5-trichlorophenoxycarbonyl, naphthyloxycarbonyl, fluorenyl-9-methoxycarbonyl, ethylthiocarbonyl, methylthiocarbonyl, butylthiocarbonyl, tert-butylthiocarbonyl, phenylthiocarbonyl, benzylthiocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, methylthiocarbonyl, butylthiocarbonyl, tert-butylthiocarbonyl, phenylthiocarbonyl, benzylthiocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl,

isopropylaminocarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2-iodoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl, 4-nitrobenzyl, 4-nitrobenzoyl, naphthylcarbonyl, phenoxyacetyl, adamantylcarbonyl, dicyclohexylphosphoryl, diphenylphosphoryl, dibenzylphosphoryl, di-(4-nitrobenzyl)phosphoryl, phenoxyphenylphosphoryl, diethylphosphinyl, diphenylphosphinyl, phthaloyl or phthalimido.

Particularly preferred amino-protecting groups are:
benzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, cyclohexoxycarbonyl, hexoxycarbonyl, octoxycarbonyl, 2-bromoethoxycarbonyl, 2-chloroethoxycarbonyl, phenoxyacetyl, naphthylcarbonyl, adamantylcarbonyl, phthaloyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloro-tert-butoxycarbonyl, menthyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloroacetyl, 2-bromoacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, phthalimido or isovaleroyl.

The compounds of the general formula (I) according to the invention have several asymmetric carbon atoms. They can occur in the D or L form independently of each other. The invention covers the optical antipodes as well as the isomeric mixtures or racemates. The groups B, D, E and F preferably occur independently of each other in the optically pure form, preferably the L form.

The compounds of the general formula (I) according to the invention can occur in the form of their salts. These can be salts of the compounds according to the invention with inorganic or organic acids or bases. The preferred acid addition products include salts with hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, or with carboxylic acids such as acetic acid, propionic acid, oxalic acid, glycolic acid, succinic

acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, adipic acid, malic acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, lactic acid, ascorbic acid, salicylic acid, 2-acetoxybenzoic acid, nicotinic acid, isonicotinic acid, or sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, naphthalene-2-sulfonic acid or naphthalene disulfonic acids.

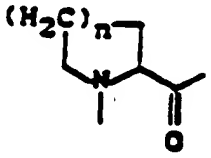
Compounds of the general formula I which are preferred for use as antiviral agents are those in which

X is hydrogen, a straight or branched alkyl or alkoxycarbonyl with up to 10 carbon atoms, naphthyl or an amine-protecting group,

A is a direct linkage

or

a residue of the formula

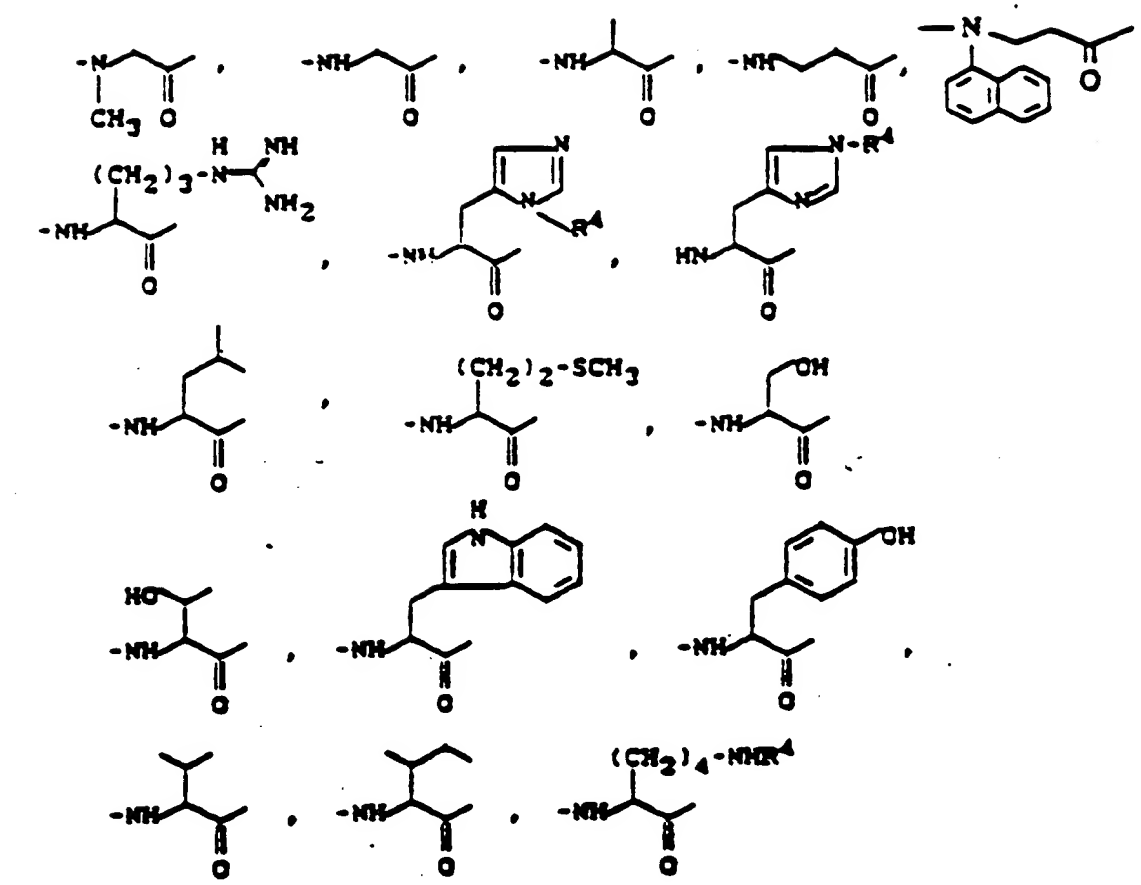


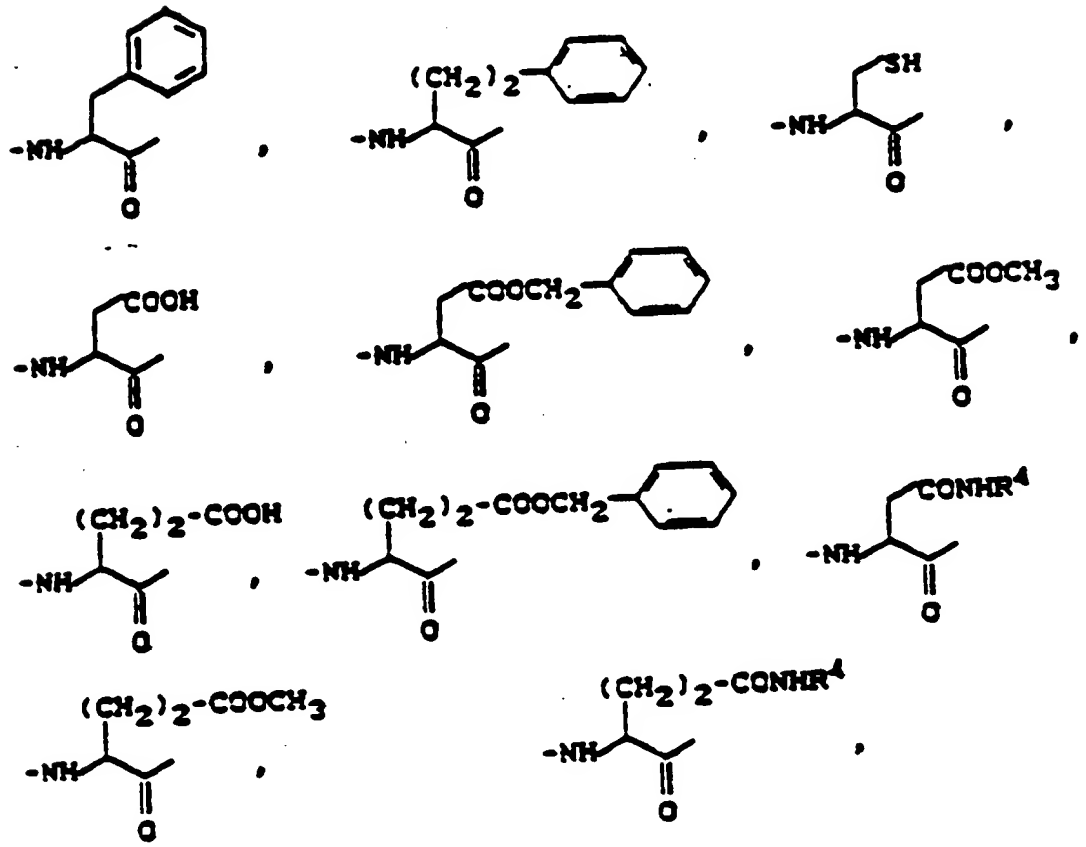
(d)

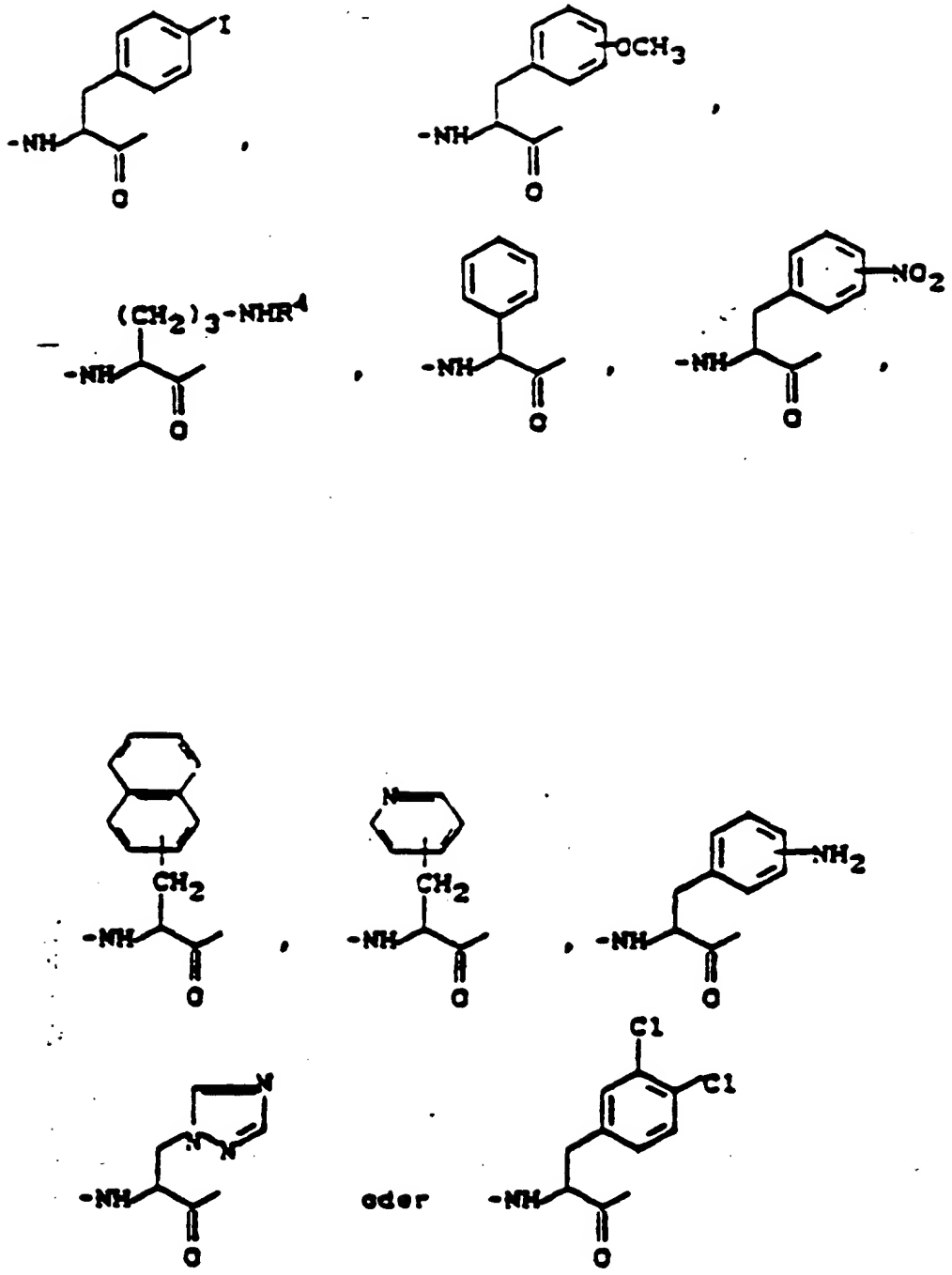
in which n is a number 1 or 2,

or

a residue of the formula:







'oder' at the end is 'or'

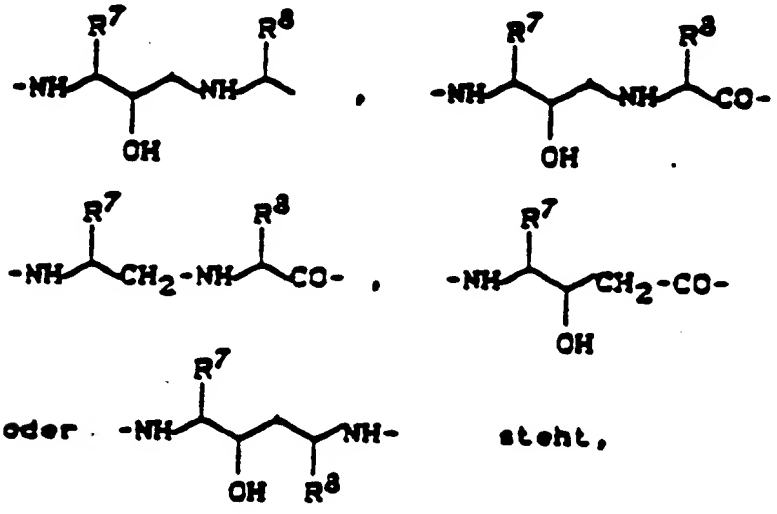
in which

R^4 is hydrogen, a straight or branched alkyl with up to 6 carbon atoms, or an amine-protecting group;

B, E, and F are the same or different and have the meaning stated above for A, and are the same as A or different from it, in their D form, L form, or DL isomeric mixture, preferably in the L form, and

D has the meaning stated above for A, and is the same as A or different from it, in the D form, L form, or DL isomeric mixture, with the provision that D may not be a direct linkage and may not represent asparagine (Asp).

Y is a group of the formula



(f)

(oder = or)

in which

R^7 is a straight or branched alkyl with up to 10 carbon atoms, which may be substituted by cyclopropyl, cyclopentyl, cyclohexyl, phenyl, hydroxy, or pyridyl,

R^8 is hydrogen, a straight or branched alkyl with up to 6 carbon atoms, which may be substituted by hydroxy or by phenyl, which itself is substituted by nitro, cyano or hydroxy.

Z is an amino-protecting group,

or a straight or branched alkyl or alkoxy with up to 8 carbon atoms, which may be substituted by hydroxy, phenyl or pyridyl,

or a group of the formula $-NR^9R^{10}$ or $-COR^{11}$

in which

R^9 and R^{10} are the same or different,

and are hydrogen,

or a straight or branched alkyl or alkenyl with up to 8 carbon atoms, which may be substituted by pyridyl or hydroxy,

or piperidinyl, piperazinyl or morpholinyl, which may be substituted by benzyl or pyridyl,

R^{11} is a straight or branched alkyl with up to 6 carbon atoms, which may be substituted by pyridyl or by a group with the formula $-NR^9R^{10}$, in which R^9 and R^{10} have the meanings stated above,

or

adamantyl, or

piperidinyl, piperazinyl or morpholinyl, which may be substituted by benzyl.

Compounds of the general formula (I) which are especially preferred for use as antiviral agents are those in which

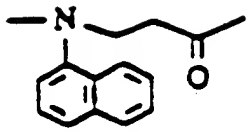
X is hydrogen

or a straight or branched alkoxycarbonyl with up to 8 carbon atoms

or napththyl or an amine-protecting group;

A is a direct linkage,

or is a residue of the formula



(g)

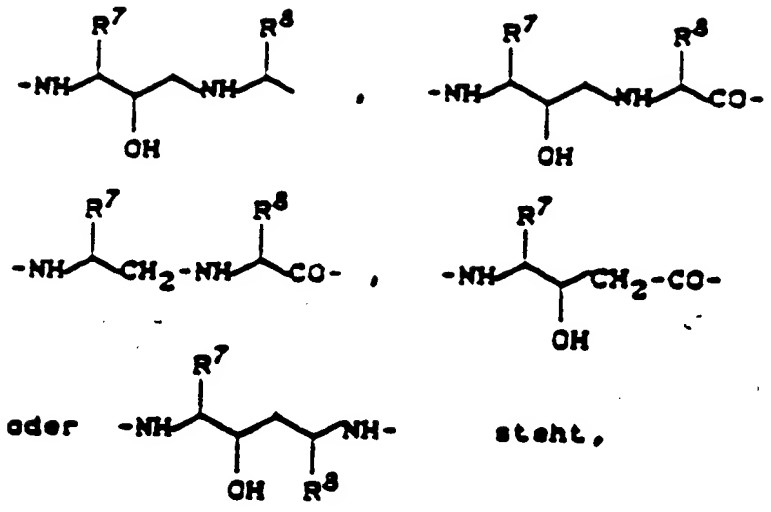
or is prolyl (Pro), glycyl (Gly), alanyl (Ala), β-alanyl (β-Ala), arginyl (Arg), histidyl (His), asparagine (Asn), leucyl (Leu), isoleucyl (Ile), seryl (Ser), threonyl (Thr), tryptophyl (Trp), tyrosyl (Tyr), valyl (Val), lysyl (Lys), asparagyl (Asp), glutamyl (Glu), glutaminamido (Gln), cystyl (Cys), methionyl (Met), phenylalanyl (Phe), 2-, 3- or 4-nitrophenylalanyl, 2-, 3-, or
4-aminophenylalanyl or pyridylalanyl, which may be substituted by the residue R^4, in which

R^4 is hydrogen, a straight or branched alkyl with up to 4 carbon atoms or an amine-protecting group;

B, E and F are the same or different, and have the meaning stated above for A, and are the same as A or different from it, in their D form, L form, or isomeric mixture, preferably in the L form,

D has the meaning stated above for A, and is the same as A or different from it, in its D form, L form or DL isomeric mixture, with the provision that D may not represent a direct linkage and may not represent asparagine (Asn).

Y is a group of the formula



(h)

(oder = or)

in which

R^7 is a straight or branched alkyl with up to 6 carbon atoms, which may be substituted by cyclohexyl or phenyl,

R^8 is hydrogen, or a straight or branched alkyl with up to 4 carbon atoms, which may be substituted by hydroxy and/or phenyl, which itself may be substituted by nitro,

Z is an amine-protecting group,
or a straight or branched alkyl or alkoxy with up to 6 carbon atoms, which may be substituted by hydroxy, phenyl or pyridyl,
or a group of the formula $-NR^9R^{10}$ or $-COR^{11}$
in which

R^9 and R^{10} are the same or different , and are
hydrogen or a straight or branched alkyl or alkenyl with up to 6 carbon atoms, which may be substituted by pyridyl or hydroxy,
or piperidinyl or piperazinyl, which may be substituted by benzyl,

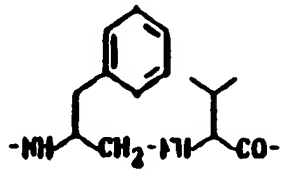
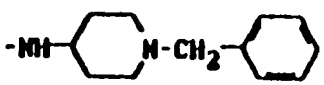
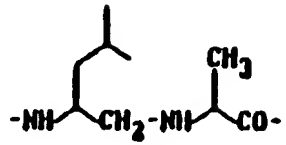
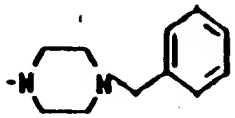
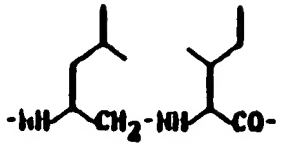
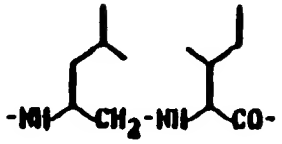
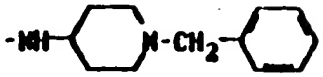
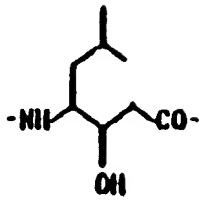
R^{11} is a straight or branched alkyl with up to 4 carbon atoms, which may be substituted by pyridyl or by a group of the formula $-NR^9R^{10}$, in which

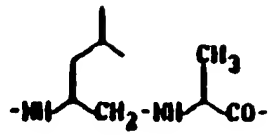
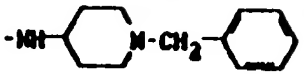
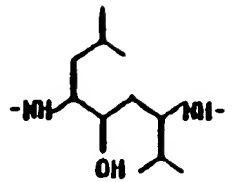
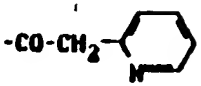
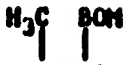
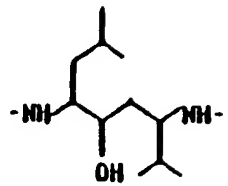
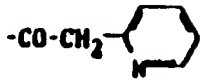
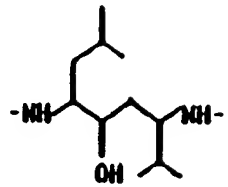
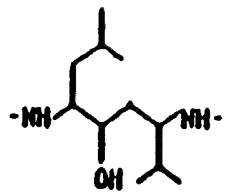
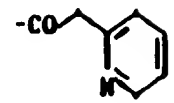
R^9 and R^{10} have the meanings stated above,

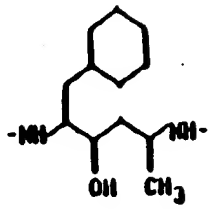
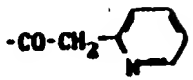
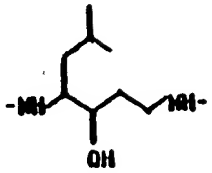
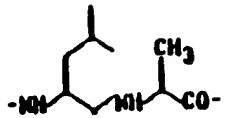
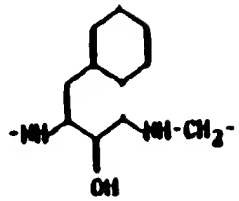
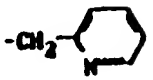
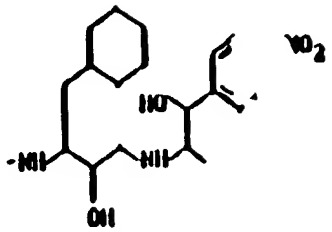
or adamantyl, or for piperidinyl or piperazinyl, which may be substituted by benzyl.

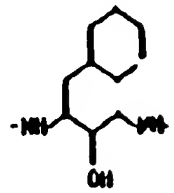
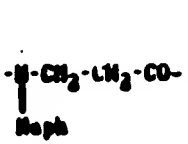
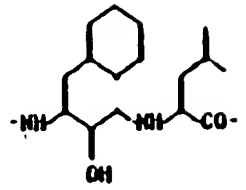
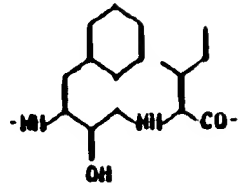
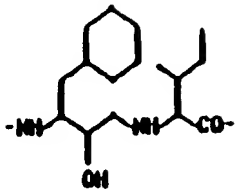
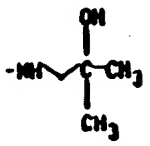
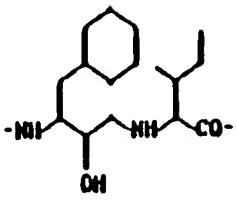
The peptides listed in Table 1 are very specially preferred for application as antiviral agents:

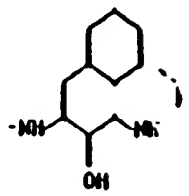
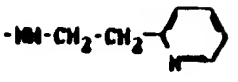
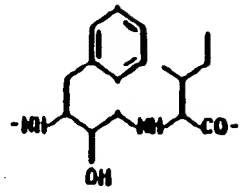
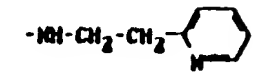
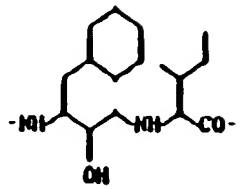
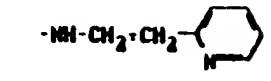
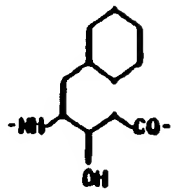
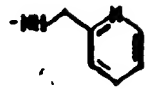
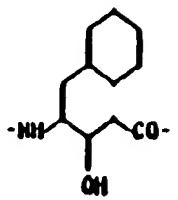
Column heading: Bsp.-Nr. = Example No.

Bsp.-Nr.	X	A	B	D	T	E	F	Z
1	Boc	Pro	Phe	His		Ile	-	
2	Boc	Pro	Phe	His		Ile	-	
3	Boc	-	Boc-His	Boc-His		Ile	-	
4	H	-	-	His		Ile	-	
5	Boc	-	Phe	His		Leu	-	$-OCH_3$

Bsp.-Nr.	X	A	B	D	Y	E	F	Z
6	Boc	-	-	-		Ile	-	
7	Boc	-	Phe	His		Leu	-	
8	Boc	-	-			Leu	-	
9	Boc	-	Phe	His		-	-	
10	Boc	Pro	Phe			L	-	

Bsp.-Nr.	X	A	B	D	Y	E	F	Z
11	Boc	Pro	Phe	Hle		Leu	-	
12	Boc	-	Phe	Hle		-	-	Adamantyl
13	H	-	-	-		Ile	-	
14	Boc	-	Phe	Hle		-	-	
15	Boc	-	Phe	Hle		-	-	$-CH_2-OH$

Bsp.-Nr.	X	A	B	D	Y	E	F	Z
16	Boc	-	Phe	Nle		-	-	$-NH_2$
17		-		Phe		-	-	$-NH_2$
18	Boc	-	Phe	Ile		-	-	
19	Boc	-	Phe	Nle		-	-	
20	Boc	-	Phe	Nle		-	-	

Bsp.-Nr.	X	A	B	D	Y	E	F	Z
21	Boc	-	Phe	His		-	-	
22	Boc	-	Phe	His		-	-	
23	Boc	-	-	-		-	-	
24	Boc	-	-	His(Boc)		Ile	-	
25	H	-	-	-		Ile		$-OCH_3$

Abbreviations in the Table:

BOC	=	tert-butoxycarbonyl
Ile	=	Isoleucine
Phe	=	Phenylalanine
His	=	Histidine
Pro	=	Proline
Leu	=	Leucine
Naph	=	Naphthyl
BOM	=	Benzyloxymethyl.

The substances according to the invention, and processes for their production, are known [see PCT WP 88102374; EP-A 201 81 071; EP-A 201 32 304, and EP-A 2011 72 347.].

Surprisingly, it was found in the investigations that led to this invention, that the compounds of the general formula (I) to be applied according to the invention have an unusually strong action against retroviruses. That was shown, for example, by the experimental data reported below for effect of the compounds on Visna virus in cell cultures. Visna virus and HIV virus (human immunodeficiency virus) are both in the retrovirus subfamily of the Lentiviruses [Haase, A. T., Nature 322:130-136(11986)]. Both viruses exhibit similar genome organization and transcription pattern with respect to the other retroviruses [Sonijo, P., et al., Cell 42:369-382(1985);
Davis, J. L. et al., Journal of Virology 61(5):1325-1331(1987)].

It has also been shown [Frank, K. B. et al., Antimicrobial Agents and Chemotherapy, 31(9):1369-1374(11987)] that known inhibitors of HIV also inhibit the Visna virus in comparable concentrations. That is, this model is suitable for testing and discovering HIV inhibitors.

In cell cultures infected with Visna virus, distinct virus-induced cytopathic effects occur 5 to 10 days after the infection. The appearance of these cytopathic effects could be prevented by treating the infected cell cultures with the compounds according to the invention.

The Visna virus test was carried out by the method of O. Narayan et al., Journal of Infectious Diseases 135(5) illegible - 806 (illegible)]. In the test, the compounds according to the invention were diluted to nontoxic concentrations in 96-well microtiter plates. Then fibroblasts [illegible] x 10^4 cells/dish) were added to each dish in production medium. Each [illegible] 50 μl of a Visna virus solution with a titer of ca. 2.5 x 10^4 $TCID_{50}$ (TCID = tissue culture infective dose). This virus dose corresponds to a MOI (multiplicity of infection) of ca. 0.05.

Under these conditions of infection, a virus-induced cytopathic effect occurred between Day 5 and Day 10 in an infection control without added substance. The infected and treated cells and the control cells were incubated for 7 days at 37°C with 5% CO_2.

When virus-induced cytopathic effects appeared in the untreated virus control the cultures were fixed with formalin and then stained with Giemsa solution. The inhibitory concentration (IC_{50}) was determined microscopically as the concentration at which the cytopathic effect was reduced by 50% in comparison with the untreated virus control, which showed 100% cell destruction.

It was found that the compound from Example 20, for instance, protects Visna virus-infected cells from the virus-induced cell destruction.

Table 2

Example No.	IC_{50} (M)
7	6.1×10^{-5}
15	1.6×10^{-4}
20	5×10^{-5}

The compounds to be applied according to the invention are, therefore, valuable agents for treatment and prevention of diseases produced by retroviruses in human and animal medicine.

These fields are indicated, for instance, in human medicine:

1.) Treatment or prevention of human retrovirus infections

2.) Treatment or prevention of diseased caused by HIV II (human immunodeficiency virus; previously known as HTLV III/LAV) and the staged associated with it, such as ARC (AIDS-related complex) and LAS (lymphadenopathy syndrome) as well as the immune deficiency and encephalopathy caused by this virus.

3.) Treatment or prevention of HTLV I or HTLV II infection.

4.) Treatment or prevention of the AIDS carrier state (AIDS transmitter state).

Examples of indications for use in animal medicine are:

Infections with

a) Maedivisna (in sheep and goats)

b) progressive pneumonia virus (PPV) (in sheep and goats)

c) caprine arthritis encephalitis virus (in sheep and goats)

d) Zwoegerziekte virus[1] (in sheep)

e) infectious anemia viruses (of horses)

f) infections caused by feline leukemia virus

This invention also includes pharmaceutical preparations in dosage units. This means that the preparations are in the form of individual portions, e. g., tablets, coated tablets, capsules, pills, suppositories, and ampules, having an active ingredient content which is a fraction or a multiple of an individual dose. The dosage units can, for example, be 1, 2, 3 or 4 individual doses, or 1/2, 1/3 or 1/4 of an individual dose. One single dose preferably contains the amount of active ingredient that is administered in one application. It usually corresponds to one, one-half, one-third, or one-fourth of a daily dose.

Suitable nontoxic inert pharmaceutical carriers include solid, semisolid or liquid diluents, fillers and formulation aids of all types.

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[1] German p. 16, line 2: Zwoegerziekte Virus is an unfamiliar term, and could not be verified with standard reference materials.

Preferred pharmaceutical preparations include tablets, coated tablets, capsules, pills, granulations, suppositories, solutions, suspensions and emulsions, pastes, salves, gels, creams, lotions, powders and [illegible].

[illegible] capsules, pills and granulations can [illegible] the active ingredient as well as the usual [illegible] such as (a) fillers and extenders, such as starches, lactose, sucrose, glucose, [illegible] and silicic acid; (b) binders, such as carboxymethylcellulose, alginate, gelatin, polyvinylpyrollidone; (c) agents to maintain moisture content, such as glycerin; (d) disintegrants such as agar-agar, calcium carbonate and sodium carbonate; (e) dissolution delaying agents, such as paraffin;
(f) absorption accelerators such as quaternary ammonium compounds; (g) wetting agents; (h) adsorbents, such as kaolin and bentonite; and (i) lubricants such as talc, calcium and magnesium stearate and solid polyethylene glycols, or mixtures of the substances listed in 9a) to (i).

The tablets, coated tablets, capsules, pills and granulations can be provided with the usual coatings and shells, sometimes containing opacifying agents, and may also be formulated so that release of the active ingredient(s) is delayed so that it is released only or preferably in a certain part of the intestinal tract. Polymers and waxes, for example, can be used as imbedding masses for that purpose.

The active ingredient(s) can, if necessary, also be microencapsulated with one or more of the carriers listed above.

Suppositories can contain the usual water-soluble or water-insoluble carriers, such as polyethylene glycols, fats such as cocoa fat and higher esters (e. g., C_{14}-alcohol with C_{16} fatty acids) or mixtures of these substances along with the active ingredient(s).

Salves, pastes, creams and gels can contain the usual carriers, such as plant and animal fats, waxes, paraffins, starches, tragacanth gum, cellulose derivatives, polyethylene glycols,

silicones, bentonite, silica gel, talc and zinc oxide or mixtures of these substances along with the active ingredient(s).

Solutions and emulsions can contain the usual carriers such as solvents, solubilizing agents, and emulsifiers, such as water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils, especially cottonseed oil, peanut oil, corn oil, olive oil, castor oil, and sesame oil, glycerin, glycerin formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, along with the active ingredient(s).

The solutions and emulsions may be in sterile and isotonic form for parenteral application.

Suspensions may contain the usual carriers such as liquid diluents, e. g., water, ethyl alcohol, propylene glycol; suspending agents, e. g., ethoxylated isostearyl alcohol, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum meta-hydroxide, bentonite, agar-agar and tragacanth gum, or mixtures of these substances, along with the active ingredient(s).

The formulations listed can also contain coloring agents, preservatives, and additives to improve the odor and taste, such as peppermint oil and eucalyptus oil, and sweeteners, e. g., saccharin.

The active ingredients of formula (I) should preferably be in the pharmaceutical preparations listed above in a concentration of about 0.1 to 99.5% by weight, preferably about 0.5 to 95% by weight of the total mixture.

The pharmaceutical preparations listed above can also contain other pharmaceutically active ingredients along with the compounds of formula (I).

The pharmaceutical preparations listed above are produced in the usual manner by known methods, e. g., by mixing of the active ingredient(s) with the carrier substance(s).

The preparations listed can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, subcutaneously), intracisternally, intravaginally, intraperitoneally, locally (powders, salves, drops), and they can be used for therapy of infections in hollow spaces and body cavities. Suitable preparations include injection solutions, solutions and suspensions for oral therapy, gels, cast formulations, emulsions, salves or drops. Opthalmologic and dermatologic formulations, silver and other salts, ear drops, eye salves, powders or solutions can be used for local therapy. Animals can also get them through their feed or drinking water in suitable formulations. Gels, powders, tablets, delayed-release tablets, premixes, concentrates, granulations, pellets, boluses, capsules, aerosols, sprays, and inhalations can also be used in humans and animals. Furthermore, the compounds according to the invention can also be processed into other carrier materials such as plastic (plastic chains for local therapy), collagen, or bone cement.

It has generally proved advantageous in both human and veterinary medicine to administer the active ingredients of formula (I) in total amounts from about 0.5 to 500, preferably 5 to 200 mg/kg body weight per 24 hours, in necessary in the form of several individual doses, to achieve the desired result. A single administration preferably contains the active ingredient(s) in amounts of about 1 to 80, especially 3 to 30 mg/kg body weight. It may be necessary, though, to depart from the doses indicated, depending on the nature and body weight of the subject to be treated, the nature and severity of the disease, the nature of the preparation and application of the medication, and on the time or interval during which the administration is done.

In some cases, then, it may be sufficient to use less than the amount of active ingredient listed above, while in other cases the amount of active ingredient listed must be exceeded. Any expert, though, can determine the particular optimal dose and nature of administration required on the basis of his expert knowledge.

The compounds to be applied according to the invention can be given in the usual concentrations and preparations along with the feed, or with feed preparations, or with the drinking water.

Claim

Peptide of the general formula (I)

X-A-B-D-Y-E-F-Z (I)

in which

X is hydrogen,

a straight or branched alkyl chain, alkylsulfonyl or alkoxycarbonyl with up to 10 carbon atoms

or a group with the formula $-COR^1$

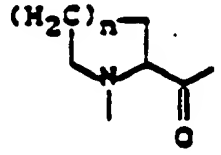
wherein

R^1 is a straight or branched alkyl chain with up to 8 carbon atoms, which may be substituted by hydroxy, amino or aryl with 6 to 10 carbon atoms, phenylsulfonyl, tolylsulfonyl, or naphthyl, or an amine-protecting group;

A is a direct linkage,

or

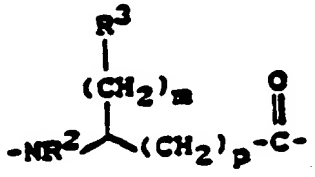
a residue of the formula



(a)

in which n is the number 1 or 2,

or a group of the formula



(b)

in which

m is a number 0, 1, 2, 3, or 4,

p is a number 0 or 1,

R^2 is hydrogen, a straight or branched alkyl chain with up to 8 carbon atoms, naphthyl or an amine-protecting group,

R^3 is hydrogen, naphthyl, halogen, carboxy, a straight or branched alkyl or alkylthio with up to 8 carbon atoms, which may be substituted by mercapto, alkylcarbonyl with up to 8 carbon atoms, hydroxy or halogen, or a group of the formula $-CH_2-NHR^4$ in which

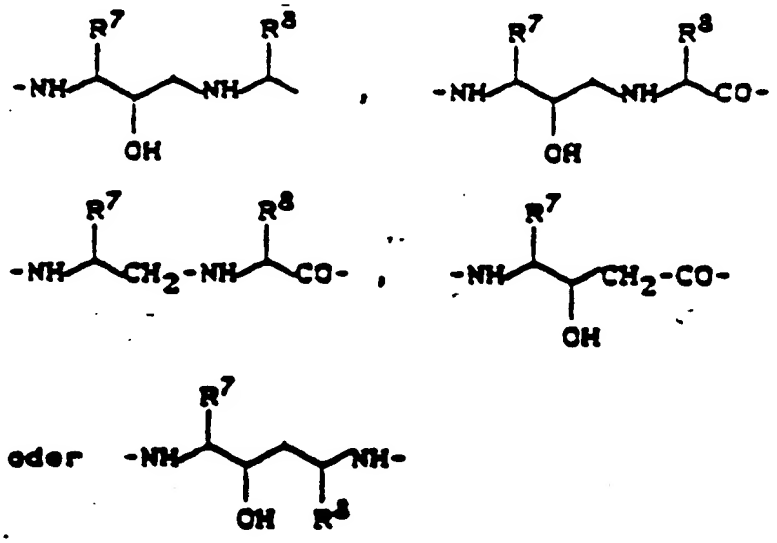
R^4 is hydrogen, a straight or branched alkyl or alkylsulfonyl with up to 8 carbon atoms, phenylsulfonyl or an amine-protecting group, guanidino, indolyl, imidazolyl, pyridyl, triazolyl or pyrazolyl, which may be substituted by R^4, in which R^4 has the meaning stated above, aryl with 6 to 10 carbon atoms, which may have up to three identical or different substituents of straight or branched alkyl or alkoxy with up to 8 carbon atoms, halogen, hydroxy, nitro, or by a group with the formula $-NR^5R^6$ in which

R^5 and R^6 are the same or different, and are hydrogen or a straight or branched alkyl with up to 8 carbon atoms,

B, E, and F are the same or different, and have the meaning stated above for A, and are the same as A or different from it, in the D form, L form, or the DL isomeric mixture, preferably in the L form, and

D has the meaning stated above for A and is the same as A or different from it, in its D form, L form, or the DL mixture, with the provision that D may not represent a direct linkage and may not represent Asparagine (Asp),

Y is a group of the formula



(c)

(oder = or)

in which

R^7 is a straight or branched alkyl chain with up to 12 carbon atoms, which may be substituted by cycloalkyl with 3 to 8 carbon atoms, aryl with 6 to 10 carbon atoms, halogen, hydroxyl, nitro, or a saturated or unsaturated 5 to 7 membered heterocycle with up to 4 heteroatoms from the series oxygen, sulfur or nitrogen,

or

aryl with 6 to 10 carbon atoms, which may be substituted by halogen, nitro, hydroxyl, cyano, straight or branched alkyl or alkoxy with up to 8 carbon atoms, or by a group with the formula $-NR^5R^6$, in which R^5 and R^6 have the meanings stated above,

R^8 is hydrogen,

straight or branched alkyl with up to 8 carbon atoms, which may be substituted by hydroxy, cycloalkyl with 3 to 8 carbon atoms, and/or aryl with 6 to 10 carbon atoms which itself may be substituted by nitro, cyano or hydroxy,

Z is an amine-protecting group,

a straight or branched alkyl or alkoxy with up to 10 carbon atoms, which may be substituted by hydroxy, phenyl or pyridyl,

or

a group of the formula $-NR^9R^{10}$ or $-COR^{11}$ in which

R^9 and R^{10} are the same or different and are hydrogen,

straight or branched alkyl or alkenyl with up to 10 carbon atoms, which may be substituted by pyridyl or hydroxy,

or

a saturated 5 to 7-membered heterocycle with up to 3 heteroatoms from the series Sulfur, oxygen or nitrogen, which may be substituted by benzyl or phenyl,

R^{11} is a straight or branched alkyl with up to 8 carbon atoms, which may be substituted by pyridyl or by a group of the formula $-NR^9R^{10}$, in which

R^9 and R^{10} have the meanings stated above,

or

adamantyl or a saturated or unsaturated 7-membered heterocycle with up to 3 heteroatoms from the series oxygen, sulfur or nitrogen, which may be substituted by benzyl,

for treatment of retroviral infections.